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The Use of Simulated Amniotic Fluid in Preventing Feeding Intolerance and

Necrotizing Enterocolitis

NURS 8000
Scholarly Project
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December 16, 2011
Introduction

The incidence of prematurity has risen drastically over the last twenty-five years. Premature deliveries are the leading cause of neonatal morbidity and mortality in the United States. Preterm birth is defined as delivery before 37 weeks of gestation (AAP, 2007). Premature births account for over 12% of all live births in the United States, that is one in eight infants. Premature delivery is caused by multiple factors including preterm labor, premature rupture of membranes, and maternal or obstetric complications.

Advances in medical technology have contributed to smaller infants surviving past the neonatal period. Nonetheless, there are many complications that accompany being born prematurely, including infection, chronic lung disease, intraventricular hemorrhage, retinopathy of prematurity, apnea of prematurity, and necrotizing enterocolitis. One of the many challenges in caring for a premature infant is providing adequate enteral nutrition. Because of the concerns for feeding intolerance and the development of necrotizing enterocolitis, many healthcare institutions have the current policy of nothing by mouth (NPO) for the first 24-48 hours.

Definition and Description of the Disease

Feeding Intolerance

Feeding intolerance is a common problem seen in the neonatal intensive care unit. Mild feeding intolerance can present with symptoms of distended loops of bowel, emesis, large pre-feeding gastric residuals, diarrhea, or gross blood in the stools. More severe forms of feeding intolerance can manifest with both gastrointestinal and systemic symptoms, such as apnea and bradycardia, decreased oxygen saturations, and lethargy (Smith, 2011). Many physicians will treat feeding intolerance by making the infant NPO and starting parenteral nutrition using total parenteral nutrition. Withholding feedings for an extended period of time can lead to the prolonged exposure to TPN and intestinal atrophy. Intestinal atrophy is associated with being NPO because the lack of enteral nutrition results in a lack of trophic hormone stimulation, luminal starvation, and intestinal atrophy. These gastrointestinal (GI) changes can disrupt the barrier function of the GI tract and can increase the bacterial translocation in the GI tract and impair immune function. This can lead to the development of necrotizing enterocolitis (NEC). Figure 2 below shows different amounts of intestinal atrophy of patients on parenteral nutrition with no or little enteral nutrition in images A, B, and C. Image D is healthy intestinal villi of a patient on enteral feedings.
Figure 2

Progressively lower amounts of caloric delivery resulted in progressively greater degrees of mucosal atrophy. A: Very Low PN intestine villus; B: Reduced PN; C: Full PN and D: Enteral control. Photomicrographs are taken at 40 × magnification.

Necrotizing Enterocolitis

Necrotizing enterocolitis (NEC) is the most common GI emergency encountered in the premature and critically ill infant. NEC is an acquired disease marked by intestinal inflammation, with or without bowel necrosis, in the absence of any mechanical intestinal obstruction (Schurr, 397, 2008). Multiple factors including infection, activation of inflammatory mediators, circulatory instability, and enteral feedings are believed collectively to cause injury to the intestinal mucosa, predisposing the infant gut to NEC development (Schurr, 397, 2008). Up to 12% of very low birth weight infants (less than 1500 grams) are affected by NEC.

The timing of the presentation of NEC is directly related to the gestational age of the infant. Term infants are at risk for developing NEC within the first few days of birth, whereas preterm infants usually develop NEC at
approximately three weeks of age. The staging system for NEC was developed by Bell and associates in 1978. The first stage of NEC, or Stage I, is suspected NEC. This stage includes symptoms of temperature instability, lethargy, apnea and bradycardia, increased gastric residuals, mild abdominal distention, emesis, and bloody stools. Radiographic findings show intestinal distention and mild ileus. Stage II is definite NEC and symptoms of this stage include all the symptoms of stage I along with marked abdominal distention and gross gastrointestinal bleeding. Radiographic findings show significant intestinal distention with an ileus, small bowel separation, fixed loops of bowel, pneumatosis intestinalis, and portal venous air. The final stage of NEC is classified as Stage III and is advanced NEC. Symptoms of this stage include all the symptoms of stage I along with deterioration of vital signs and evidence of septic shock. Radiographic findings will be the same of stage II with possible evidence of gastrointestinal perforation and pneumoperitoneum.

Treatment of NEC includes keeping the infant nothing by mouth (NPO), obtaining serial abdominal radiographs, and gastric decompression. Blood cultures are drawn to rule out systemic infection. Broad-spectrum antibiotics are started after blood cultures are drawn. Studies have shown that 41% of NEC infants undergo surgical treatment. This treatment consists of peritoneal drainage and/or laparotomy for resection of the necrotic bowel (Schurr, 2008).

**Modified Bell’s Staging Criteria for Necrotizing Enterocolitis**

<table>
<thead>
<tr>
<th>STAGE</th>
<th>SYSTEMIC SIGNS</th>
<th>INTESTINAL SIGNS</th>
<th>RADILOGIC SIGNS</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Suspected</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Temperature instability, apnea,</td>
<td>Elevated pregaavage residuals, mild</td>
<td>Normal or mild ileus</td>
<td>NPO, antibiotics x 3 days</td>
</tr>
<tr>
<td></td>
<td>bradycardia</td>
<td>abdominal distention, occult blood in</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>stool</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Same as IA</td>
<td>Same as IA, plus gross blood in stool</td>
<td>Same as IA</td>
<td>Same as IA</td>
</tr>
<tr>
<td>II. Definite</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A: Mildly ill</td>
<td>Same as IA</td>
<td>Same as I, plus absent bowel sounds,</td>
<td>ileus, pneumatosis intestinalis</td>
<td>NPO, antibiotics x 7 to 10 days</td>
</tr>
<tr>
<td>B: Moderately ill</td>
<td>Same as I, plus mild</td>
<td>abdominal tenderness</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>metabolic acidosis, mild</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>thrombocytopenia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III. Advanced</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A: Severely ill, bowel intact</td>
<td>Same as IIB, plus hypotension, bradycardia, respiratory acidosis, metabolic acidosis, disseminated intravascular coagulation, neutropenia</td>
<td>Same as I and II, plus signs</td>
<td>Same as IIB, plus definitive NPO, antibiotics x 14 days, fluid resuscitation, isotropic support, ventilator therapy, paracentesis</td>
<td></td>
</tr>
<tr>
<td>B: Severely ill, bowel perforated</td>
<td>Same as IIIA</td>
<td>Same as IIIA</td>
<td>Same as IIB, plus pneumoperitoneum</td>
<td>Same as IIIA, plus surgery</td>
</tr>
</tbody>
</table>
Long term complications of NEC include feeding intolerance, bowel obstructions, and short-gut syndrome.

**Amniotic Fluid**

Amniotic fluid is the physical buffer and barrier to the outside world, along with providing for fetal nutritional requirements and playing a significant role in fetal gut maturation and development. “The human fetus swallows over 200mL of amniotic fluid per kilogram of weight each day and such swallowing is essential for normal small bowel development (Lima-Rogel et al, 297, 2004).” If a fetus fails to swallow amniotic fluid, the small bowel mucosa will develop in a disorganized and rudimentary manner (Barney, 2006). During the use of hyperalimentation, many infants are restricted to nothing by mouth. Disuse atrophy of the small bowel mucosa, following several days of enteral fasting, is a factor that might contribute to, or delay recovery from, feeding intolerance among premature infants (Barney, 2006). Intestinal villous atrophy occurs during a period of NPO status in an infant. This atrophy can occur in as little as 24 to 72 hours and results in the loss of intestinal villous structure and function. It is the assumption of medical personal that using a simulated amniotic fluid solution after bowel surgery will help to restore the villous structure and function of the intestinal tract and will help reduce any feeding intolerance. It was originally thought that the volume of amniotic fluid being swallowed was what helped the growth, development, and maturation of the intestinal tract. Numerous research studies using a simulated amniotic fluid solution, found it was the growth factors in the amniotic fluid that actually produced the growth, development, and maturation of the intestinal tract. Growth factors found in amniotic fluid, also found in colostrum and breast milk, have been shown to promote proliferation of fetal intestinal cells. These growth factors include epidermal growth factor, insulin-like growth factor 1, transforming growth factor alpha, and hepatocyte growth factor. Other growth factors specific to amniotic fluid include recombinant human erythropoietin and recombinant human granulocyte colony stimulating factor.

Maheshwari (2003) has studied growth factors of amniotic fluid and their mechanism of action. The two main growth factors studied were erythropoietin and granulocyte colony-stimulating factor. Erythropoietin was first recognized for its antiapoptotic action on erythrocyte progenitors, but it has since been found to have many nonerythropoietic functions during human development, such as a neuroprotectant in the central nervous system and enhancing the development of the fetal gastrointestinal mucosa. Granulocyte colony-stimulating factor was first
recognized for its capacity to support the clonal maturation of neutrophils, but was later found to have important developmental actions on fetal enterocytes (Christensen et al, 2005).

Swallowing amniotic fluid enhances the fetal gastrointestinal tract development and in late gestation, amniotic fluid accounts for 10-14% of the nutritional requirements of the normal fetus (Underwood, 2006). Amniotic fluid and human milk both contain growth factors that exert prenatal and postnatal effects on intestinal and somatic growth in the fetus and the newborn. Insulin-like growth factor I (IGF-I) is the primary mediator of both intrauterine and postnatal growth in mammals. Studies have shown that IGF-I increases fetal intestinal growth, increases fetal plasma IGF-I concentrations, and increases the maturity of fetal enterocytes. Epidermal growth factor (EGF) is a small peptide that stimulates cell mitosis and differentiation. EGF increases DNA and glycoprotein synthesis in human fetal gastric cells, this leads to an increase in small intestinal length and intestinal villus height (Underwood, 2006). These growth factors are essential for proper growth and development of the intestinal villi.

Literature Review

Databases searched included Academic Search Premier, CIHANL, MEDLINE, and Google Scholar. Search parameters included keywords of feeding tolerance and amniotic fluid. The search was limited by using only research articles. Research studies were found in journals of American Journal of Clinical Nutrition, Neonatal Network, Journal of Perinatology, and American Journal of Pediatrics. The purpose of these studies was to evaluate the use of simulated amniotic fluid feedings in infants with feeding intolerance and necrotizing enterocolitis.

Lima-Rogel et al (2003) conducted a study to evaluate the tolerance of using a sterile isotonic electrolyte solution containing recombinant growth factors in infants recovering from necrotizing enterocolitis. Three different study groups were given different amounts of the same isotonic electrolyte solution, these amounts included 5, 10, and 20mL/kg/day of fluid. A p-value of <0.05 was considered statistically significant. None of neonates who received the study solution had the administration of the study fluid prematurely discontinued and none required surgery for NEC. No clinical significance was found between the three test groups. The researchers stated each of the neonates tolerated the study solution without any observed adverse effects during the study or in the week following the study. The P values obtained included P = 0.694, P = 0.873, and P = 0.339 respectively. The authors
concluded there was no intolerance among the 30 patients. Further research was recommended to examine the safety, effectiveness, and benefit to risk ratio to improve feeding tolerance of neonates recovering from NEC.

Another study by Lima-Rogel et al (2004) was conducted to evaluate the tolerance of an enterally administered simulated amniotic fluid-like solution by neonates recovering from surgery for congenital bowel abnormalities. The authors explain that two previous phase I studies with this solution only involved a three day period of administration, but reasoned that infants with congenital surgical abnormalities would have abnormal intestinal villi that might require longer periods of administration if any salutary effect could be expected. This trial was to test the simulated amniotic solution for more than three days to assess tolerance. The hypothesis was clearly stated. Inclusion and exclusion criteria were defined. Parental consent was obtained and IRB approval was given before the trial started. Final conclusions indicated the test solutions were well tolerated and all test subjects reached full enteral feedings by 14 days or fewer after the experimental solution was begun.

Barney et al (2006) performed a study to treat feeding intolerance using an enteral solution patterned after human amniotic fluid. The authors explain that previous trials using this solution suggested that it is well tolerated when administered at a dose of 20mL/kg/day. This study was a randomized, controlled, masked trial of 20 NICU patients who had manifestations of feeding intolerance. The subjects in this trial received either the test solution or a sham solution before enteral feedings were started, once milk feedings were ordered, the test or sham solutions were given with the milk feedings. Inclusion and exclusion criteria were defined. Parental consent was obtained. Final conclusions remained indeterminate for this trial and authors stated they predict that a solution like the one tested will be helpful only in cases where the intestinal mucosa had undergone significant atrophic changes, amenable to topical growth factor treatment.

Christensen et al (2005) performed a study to determine if feeding a simulated amniotic fluid to low birth weight infants would reduce feeding intolerance. The authors explain the previous trial found the test solution was tolerated every three hours for a period of 72 hours. This study was a comparison trial involving enteral caloric intake between patients who received the simulated amniotic fluid and those who did not. The population included 20 neonates who had birth weights between 750 grams and 1250 grams. Written parental consent was obtained and approval was given by the IRB before initiation of the study. Seven of the ten recipients receiving the test solution were given all required doses. In the remaining three recipients, doses of the test solution were either held
intentionally due to large prefeeding gastric residuals, or inadvertently with a skipped dose. One patient had all feeding held for 48 hours due to a “rule out sepsis” episode. The overall result of this study showed a significant increase in enteral calories tolerated when using the test solution with $P < 0.05$. Also a significant increase in weight increase in the patients receiving the test solution with $P < 0.05$. The authors stated they could not determine whether the test solution did indeed reduce feeding intolerance among low birth weight neonates. Final conclusions of the authors were that the information on enteral intake of these study subjects would be useful in planning a randomized control trial and the results of this pilot study suggest that a randomized trial to test the effectiveness of this solution in preventing feeding intolerance would be worthwhile.

The final study by Sullivan et al (2002) was done to assess the tolerance of using simulated amniotic fluid enterally administered in preterm neonates. The inclusion and exclusion were defined. The study was approved by the IRB and informed parental consent was obtained. A $P$ value of $<0.05$ was considered statistically significant. This study consists of three groups of 10 patients each. The groups received different dosing amounts of simulated amniotic fluid of 5mL/kg/day, 10mL/kg/day, and 20mL/kg/day. Dosing of the simulated amniotic fluid was discontinued in three patients during the study, one from each dosing group. The first patient had dosing discontinued after 20 doses of simulated amniotic fluid due to gastric residuals, one patient after 3 doses because of stage 1 NEC, and the last patient after 5 doses because of symptomatic patent ductus arteriosus. The outcome and comovements, the total change in abdominal girth, the number of episodes of emesis, occurrence of hypotension or hypertension, development of NEC, occurrence of rashes, and the number of deaths. The overall results showed the 5mL and 10mL groups had the number of gastric residuals significantly increase with $P = 0.038$. There was an increase in bowel movements in the 10mL and 20mL groups with $P = 0.004$. There was no difference between the dosing groups related to number of gastric residuals with $P = 0.28$. There was no difference between dosing groups related to the number of bowel movements with $P = 0.76$. The authors conclude their measurements of tolerance suggested the preparation appears to be safe and well tolerated in doses less than or equal to 20mL/kg/day for three consecutive days. They stated the number of residuals and bowel movements were increased in the days following administration of the simulated amniotic fluid compared with the number of each during the period of fluid administration. It is likely that the initiation of feeds with the accompanying increase in volume contributed to the increase bowel activity and number of residuals observed after feedings.
The literature reviewed has shown that this test solution of simulated amniotic fluid has been considered safe and is well tolerated among study recipients. The authors of these studies have stated that further testing will be required in order to confirm if this solution does in fact reduce feeding intolerance and the incidence of necrotizing enterocolitis.

Recommendations For Practice

The purpose of this review was to critically appraise the literature regarding the use of simulated amniotic fluid in preventing feeding intolerance and necrotizing enterocolitis. Investigations reviewed demonstrated that the simulated amniotic fluid is well tolerated among premature infants and those infants recovering from necrotizing enterocolitis. When neonates are born prematurely, the swallowing of amniotic fluid stops abruptly. During the first days of life, small, ill neonates often remain NPO for several days. Before feedings are started in these patients, small trophic feedings are helpful in reducing feeding intolerance. Unfortunately the amount of granulocyte colony-stimulating factor and erythropoietin provided by trophic feedings are extremely small, when compared to the amounts received in utero from swallowing amniotic fluid. In an attempt to decrease the incidence of feeding intolerance associated with the villous atrophy and luminal starvation that occur when a premature or critically ill infant is made NPO, Calhoun and associates (2000) initiated studies on the enteral administration of a simulated amniotic fluid solution. Many researchers have established that enteral supplementation of some of the growth factors found in amniotic fluid is well tolerated in NICU patients. The ideal simulated amniotic fluid study would compare feeding tolerance and growth during and after the continuous administration of simulated amniotic fluid to the infant until a corrected gestational age of 40 weeks or term (Smith, 113, 2011).

Prevention and treatment of feeding intolerance and necrotizing enterocolitis is instrumental in providing optimal enteral nutrition to allow appropriate growth and development of infants. Second to prematurity, feedings and feeding practices are frequently implicated in the development of necrotizing enterocolitis (Schurr, 2008). Research studying prevention of necrotizing enterocolitis and feeding tolerance should be directed using simulated amniotic fluid. The use of standardized feeding guidelines and breast milk are the only feeding practices that have been shown consistently to reduce NEC (Schurr, 404, 2008). Delaying feedings in an attempt to eliminate necrotizing enterocolitis and feeding intolerance may result in other complications. Trophic feedings of breast milk is the one measure of prevention proven by research to stimulate the developing gastrointestinal tract. The research
that has been conducted shows that simulated amniotic fluid is well tolerated. With this research, fetuses could continue to swallow amniotic fluid as infants, to prevent intestinal atrophy, which leads to feeding intolerance and necrotizing enterocolitis.

Implications For Nursing Practice

One of the most critical issues of premature infants is feeding intolerance and the development of necrotizing enterocolitis. Feeding intolerance often results in the order to keep the infant NPO, which can lead to disuse atrophy of the intestine. Medical professionals must strive to find ways to reduce the incidence of feeding intolerance and provide these infants with sufficient enteral intake to sustain proper growth and development. Small enteral feedings using human breast milk or premature infant formula has been used in the past to avoid disuse atrophy of the small bowel mucosa and to try to prevent feeding intolerance. Unfortunately the amount of granulocyte colony-stimulating factor and erythropoietin provided by trophic feedings are extremely small, when compared to the amounts received in utero from swallowing amniotic fluid. By providing enteral feedings of simulated amniotic fluid, nurse practitioners would be able to provide infants with the needed granulocyte colony-stimulating factor and erythropoietin to induce intestinal DNA synthesis and cell growth of the intestinal tract.

Family Education

An infant diagnosed with feeding intolerance or necrotizing enterocolitis can be a very scary situation for the parents. Parents should always be informed of the change in their infant’s status as soon as possible after the infant has been stabilized. The capacity of the parents to retain and assimilate information is generally limited for a time following the initial diagnosis. During the initial stage of shock and disbelief, only information regarding the immediate condition of the infant should be given to the parents. Physicians, nurse practitioners, and nurses should be cognizant of the parents’ readiness to learn and accept new information. When immediate surgical intervention is needed, and the infant must transfer to another facility that provides these services every, effort should be made to keep the family together. The stress parents feel when separated from their infant is then compounded when they are separated from each other. Relaying and explaining information to the parents regarding the status of their infant, will keep the mother and father updated and help facilitate the bonding process. Frequent updates to the parents and
the opportunity to answer questions is of particular importance when information is being offered from multiple personnel with a variety of perspectives and approaches to care.

Conclusion

Feeding intolerance is frequently encountered in the neonatal intensive care unit. Current treatment for feeding intolerance is to discontinue enteral feedings, which can lead to intestinal atrophy. Intestinal atrophy can lead to the formation of necrotizing enterocolitis. An evaluation of the literature has shown that there is no specific therapy to prevent feeding intolerance and necrotizing enterocolitis. The use of simulated amniotic fluid is a promising therapy that promotes the growth and development of normal intestinal tissue. Clinical trials to date have shown this solution to be well tolerated, though larger randomized control trials are needed to determine if the solution will significantly reduce the incidence of feeding intolerance and necrotizing enterocolitis.
References


Smith, C.G. (2011). In the critically ill, nothing-by-mouth infant, would enteral administration of simulated amniotic fluid improve feeding tolerance compared with the current practice of no therapy? An evidence-based
